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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/812,269	03/20/2001	David Gurley	A1934-2 US	2812

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EXAMINER	
FISHER, LATONIA M	
ART UNIT	PAPER NUMBER
1623	2

DATE MAILED: 04/08/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/812,269	GURLEY ET AL.	
	Examiner	Art Unit	
	La Tonia M. Fisher	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2 and 29-60* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2 and 29-60* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *1* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Claims 1-2 and 29-60 are pending. Claims 3-28 are cancelled.

Title

The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-2 and 29-33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Qian et al. (USPN 6,077,846) in view of Krause et al., *Ivermectin: A Positive Allosteric Effector of the α7 Neuronal Nicotinic Acetylcholine Receptor,* Molecular Pharmacology, 53:283-294 (1998), Kooyman et al., *5-Hydroxyindole Slows Desensitization of the 5-HT3 Receptor*, Br. J. Pharmacol. 108:287-289 (1993) and Schrattenholz et al., *Agonist Responses of Neuronal*

Nicotinic Acetylcholine Receptors Are Potentiated by a Novel Class of Allosterically Acting Ligands, Molecular Pharmacology, 49:1-6 (1996).

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claim 1 is drawn to a pharmaceutical composition comprising a positive modulator of a nicotinic receptor agonist together with a pharmaceutically acceptable carrier, said positive modulator having the capability to increase the efficacy of the said nicotinic receptor agonist. Claims 2 limits claim 1 wherein the composition further comprises a nicotinic receptor agonist. Claims 29 –33, dependent on claims 1 or 2, identify the positive modulator as 5-hydroxyindole and the nicotinic receptor agonist as an α7-nicotinic receptor agonist.

Qian et al. teach methods for treating diseases that can be treated with a nicotinic agonist comprising administering an effective amount of a 7-azabicyclo-heptane or heptene compound. The diseased disclosed to be treated include a plethora of mental and cognitive disorders including cessation of smoking, Parkinson's disease, Tourette's syndrome, Alzheimer's disease, ulcerative colitis and aphthous ulcer, see USPN '846, col. 8, lines 14-23 and claims 1-3 and 5-7. Qian et al. teach that while it is possible for the active ingredient to be administered alone in the prior art invention, it is suggested that the active ingredient be administered as a pharmaceutical

formulation comprising a pharmaceutically acceptable carrier, diluent or excipient. See USPN '846, col. 1, lines 25-30.

While Qian et al. do not teach the addition of a positive modulator of a nicotinic receptor agonist in the prior art invention, Qian, et al. do suggest the use of additional agents in the prior art composition. See USPN '846, col. 10, lines 36-40.

Krause et al. teach the anthelmintic drug ivermectin strongly potentiates the ACh-evoked current of the α7 homomeric neuronal nAChRs from both chick and human. See Krause et al., p. 289, col. 2, lines 24-26. Krause et al. further disclose that ivermectin acts on the α7 nAChR as a positive allosteric effector of the neuronal nAChR. See Krause et al., p. 284, col. 2, lines 40-43. Additionally, Krause et al. disclose the specific loss of nAChR binding sites observed in the brain of patients with neurodegenerative diseases such as Alzheimer's or Parkinson's suggests that nicotinic receptors may play a critical role in the evolution of these disorders, see Krause et al., p. 284, col. 1, lines 16-19. At page 284, col. 1, lines 22-26, Krause et al. teach stimulation of nAChRs in affected patients either by selective agonists or by compounds reducing the activity of acetylcholinesterase shows positive effects on the patients' overall cognitive abilities, and a complementary approach would be to use positive allosteric effectors that could selectively enhance the activity of neuronal nAChRs.

Neither Qian et al. Krause et al. teach 5-hydroxindole as a positive modulator of a nicotinic receptor agonist.

Kooyman et al. teach 5-hydroxindole, a moiety of the 5-hydroxytryptamine (5-HT) molecule, slows agonist-induced desensitization of the 5-HT3 receptor-mediated current. See Kooyman et al., col. 1, lines 25-28. In addition, Kooyman et al. teach simultaneously with the

slowing of desensitization, the amplitude of the inward current is enhanced. See Kooyman et al., col. 1, lines 20-24.

Schrattenholz et al. teach neuronal nicotinic acetylcholine receptors are subject to positive modulatory control by allosterically acting ligands and the neurotransmitter 5-hydroxytryptamine (5-HT), when applied in submicromolar concentration with nicotinic agonists, significantly increase the frequency of opening of nicotinic receptor channels and potentiate agonist-activated currents. See Schrattenholz et al. p. 1, col. 1, lines 10-12, p.2, col. 1, lines 3-6. See also, p. 6, col. 1, lines 13-20.

Accordingly, it would have been obvious to one having ordinary skill in the art to combine a positive modulator of a nicotinic receptor agonist, particularly 5-hydroxyindole, a pharmaceutically acceptable carrier and an α7-nicotinic receptor agonist to form a third composition as Applicants have done with the references before them. The motivation to combine the individual components into a third composition is to obtain a composition intended to be used to accomplish the same purpose as the compositional components independently.

Claims 34-60 are rejected under 35 U.S.C. 103(a) as being unpatentable over Qian et al. (USPN 6,077,846) in view of Krause et al., *Ivermectin: A Positive Allosteric Effector of the α7 Neuronal Nicotinic Acetylcholine Receptor,* Molecular Pharmacology, 53:283-294 (1998) and Kooyman et al., *5-Hydroxyindole Slows Desensitization of the 5-HT3 Receptor*, Br. J. Pharmacol. 108:287-289 (1993).

Claim 34 is drawn to a method for the treatment of a condition associated with reduced nicotinic transmission by administering to a patient in need of such treatment a medically effective amount of a positive modulator of a nicotinic receptor agonist, said positive modulator

having the capability to increase the efficacy of the said nicotinic receptor agonist. Dependent limitations claimed include the addition of a nicotinic receptor agonist to the composition, the identity of the positive modulator, the identity of the nicotinic receptor, and the identity of the condition associated with reduced nicotine transmission.

Qian et al. teach methods for treating diseases that can be treated with a nicotinic agonist comprising administering an effective amount of a 7-azabicyclo-heptane or heptene compound. The diseased disclosed to be treated include a plethora of mental and cognitive disorders including cessation of smoking, Parkinson's disease, Tourette's syndrome, Alzheimer's disease, ulcerative colitis and aphthous ulcer, see USPN '846, col. 8, lines 14-23 and claims 1-3 and 5-7. Qian et al. teach that while it is possible for the active ingredient to be administered alone in the prior art invention, it is suggested that the active ingredient be administered as a pharmaceutical formulation comprising a pharmaceutically acceptable carrier, diluent or excipient. See USPN '846, col. 1, lines 25-30.

While Qian et al. do not teach the addition of a positive modulator of a nicotinic receptor agonist in the prior art invention, Qian, et al. do suggest the use of additional agents in the prior art composition. See USPN '846, col. 10, lines 36-40.

Krause et al. teach the anthelmintic drug ivermectin strongly potentiates the ACh-evoked current of the α7 homomeric neuronal nAChRs from both chick and human. See Krause et al., p. 289, col. 2, lines 24-26. Krause et al. further disclose that ivermectin acts on the α7 nAChR as a positive allosteric effector of the neuronal nAChR. See Krause et al., p. 284, col. 2, lines 40-43. Additionally, Krause et al. disclose the specific loss of nAChR binding sites observed in the brain of patients with neurodegenerative diseases such as Alzheimer's or Parkinson's suggests

that nicotinic receptors may play a critical role in the evolution of these disorders, see Krause et al., p. 284, col. 1, lines 16-19. At page 284, col. 1, lines 22-26, Krause et al. teach stimulation of nAChRs in affected patients either by selective agonists or by compounds reducing the activity of acetylcholinesterase shows positive effects on the patients' overall cognitive abilities, and a complementary approach would be to use positive allosteric effectors that could selectively enhance the activity of neuronal nAChRs.

Neither Qian et al. Krause et al. teach 5-hydroxindole as a positive modulator of a nicotinic receptor agonist.

Kooyman et al. teach 5-hydroxindole, a moiety of the 5-hydroxytryptamine (5-HT) molecule, slows agonist-induced desensitization of the 5-HT3 receptor-mediated current. See Kooyman et al., col. 1, lines 25-28. In addition, Kooyman et al. teach simultaneously with the slowing of desensitization, the amplitude of the inward current is enhanced. See Kooyman et al., col. 1, lines 20-24.

Schrattenholz et al. teach neuronal nicotinic acetylcholine receptors are subject to positive modulatory control by allosterically acting ligands and the neurotransmitter 5-hydroxytryptamine (5-HT), when applied in submicromolar concentration with nicotinic agonists, significantly increase the frequency of opening of nicotinic receptor channels and potentiate agonist-activated currents. See Schrattenholz et al. p. 1, col. 1, lines 10-12, p.2, col. 1, lines 3-6. See also, p. 6, col. 1, lines 13-20.

Thus, based on these teachings and disclosures, it would have been obvious to one having ordinary skill in the art to administer to a patient a positive modulator of a nicotinic receptor agonist, particularly, 5-hydroxyindole, with or without a α7-nicotinic receptor agonist to treat a

condition associated with reduced nicotine transmission as applicant's have done with the above cited references before them, because these references provided sufficient motivation and a reasonable expectation of success for administering a positive modulator of a nicotinic receptor agonist with or without a nicotinic receptor agonist for treating a disease or condition associated with reduced nicotine transmission.

Conclusion

Claims 1-2 and 29-60 are rejected. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to La Tonia M. Fisher whose telephone number is (703) 306-5819. The examiner can normally be reached on Monday - Friday from 9:30am to 5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James O. Wilson can be reached on (703) 308-4624. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4556 for regular communications and (703) 308-4556 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1235.

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